

Long-term results of the Medtronic Mosaic porcine bioprosthesis in the aortic position

Amedeo Anselmi, MD, Erwan Flécher, MD, PhD, Vito Giovanni Ruggieri, MD, PhD, Majid Harmouche, MD, Thierry Langanay, MD, Hervé Corbineau, MD, Jean-Philippe Verhoye, MD, PhD, and Alain Leguerrier, MD

Objective: We addressed the long-term results of the Medtronic Mosaic porcine prosthesis in the aortic position.

Methods: From 1994 to 2004, 1007 Mosaic valves were used for aortic valve replacement. The data were prospectively collected, retrospectively analyzed, and stratified according to patient age at surgery (group 1, <70 years; group 2, 70-75 years; group 3, 76-80 years; and group 4, >80 years), using both actual (cumulative risks) and actuarial methods.

Results: Operative mortality was 5% (valve related in 14%). Globally, 8122.17 patient-years were available (average follow-up, 8.5 ± 3.9 years; 99.8% complete). Overall, survival at 15 years was lower among the elderly strata ($P < .0001$). Freedom from structural valve deterioration (SVD) was 95.1% (actual) and 86.3% (actuarial; 24 SVD events). Survival free from SVD was lower in group 1 ($P = .003$) but comparable among the other groups. Overall freedom at 15 years from the composite endpoint (any valve-related adverse events) was 82% (actual) and 71.3% (actuarial). No meaningful intergroup differences were found in survival free from the composite endpoint ($P = .9$) or freedom from valve-related mortality ($P = .8$). Younger patients at surgery did not show accelerated degeneration. No relationship could be established between prosthetic size and SVD.

Conclusions: The implantation of a bioprosthesis in patients aged 70 years or older remains fully justified. The rate of SVD was higher in younger patients, mainly owing to their greater life expectancy. Patients younger than 70 can receive a bioprosthesis, provided that the correct information regarding the expected durability has been provided. This might be better accomplished through the actual methodology. (J Thorac Cardiovasc Surg 2014;147:1884-91)

Third-generation bioprostheses for aortic valve replacement are now attaining the long-term follow-up data that allow consistent evaluation of durability. The Mosaic porcine valve (Medtronic Inc, Minneapolis, Minn) was introduced in 1994. It has been the object of a multi-institutional regulatory study, which established its favorable profile in terms of safety, thromboembolic event rate, and hemodynamic performance.¹⁻⁴ The same surgical groups have recently reported on the 12-year performance of this device, including freedom from late valve-related adverse events in 797 patients who had undergone aortic valve replacement and 232 patients who had undergone mitral valve replacement.⁵ Although reporting most satisfactory freedom from structural valve deterioration (SVD) rates, these investigators underlined the need for continued

evaluation at longer follow-up intervals. In particular, additional insights are needed regarding the effects of patient age at surgery on the incidence and timing of valve-related adverse events.

The objective of the present investigation was twofold. We aimed to assess the long-term clinical results of the Mosaic prosthesis in a large single-institution series and to clarify the expected rates of SVD and other valve-related adverse events according to patient age at surgery. Our ultimate purpose was to offer useful information for preoperative decision making. Therefore, we analyzed the outcome variables using both the actual method (which provides the real incidence of valve-related complications by eliminating the censoring from competing risks) and the actuarial analysis.

METHODS

Inclusion Criteria and Management of Data

We retrospectively reviewed the electronic records of 1005 patients who had received at our institution a total of 1007 Medtronic Mosaic porcine bioprostheses from July 31, 1994, to August 1, 2004. We included all patients who had undergone aortic valve replacement using a Mosaic valve in the aortic position during the study period. The performance of any associated cardiac surgical procedure at implantation, in terms of a history of previous cardiac surgery, did not represent exclusion criteria. The perioperative clinical data were prospectively collected, as previously described.⁶ In brief, the baseline variables, intraoperative findings, and

From the Division of Thoracic and Cardiovascular Surgery, Pontchaillou University Hospital, Rennes, France.

Disclosures: Authors have nothing to disclose with regard to commercial support. Received for publication Feb 18, 2013; revisions received June 21, 2013; accepted for publication July 9, 2013; available ahead of print Aug 28, 2013.

Address for reprints: Amedeo Anselmi, MD, Division of Cardiovascular and Thoracic Surgery, Pontchaillou University Hospital, 2, rue Henri le Guilloux, Rennes 35000, France (E-mail: amedeo.anselmi@alice.it).

0022-5223/\$36.00

Copyright © 2014 by The American Association for Thoracic Surgery

<http://dx.doi.org/10.1016/j.jtcvs.2013.07.005>

Abbreviations and Acronyms

IE	= infective endocarditis
NSVD	= nonstructural valve dysfunction
SVD	= structural valve deterioration

early postoperative results for all patients undergoing cardiac surgery at the Rennes University Hospital are systematically entered in an electronic database at patient discharge. The database is regularly checked for completeness and consistency. Clinical follow-up data were collected in late 2012 by contacting the referring cardiologist of each patient. The practitioners were provided a questionnaire that included inquiries of the patient's status (occurrence of death or any other adverse event, valve related or non-valve related) and the time at which the adverse event had occurred. In the event of missing or incomplete information, the general practitioners or the patients themselves were interviewed by telephone. The definitions of valve-related events were established in compliance with the current recommendations.⁷ SVD was defined as dysfunction or deterioration of the prosthesis (excluding infection or thrombosis) evident on echocardiography and/or at reoperation. The cause of death was determined by review of the instrumental and hospital records. Any death from unknown causes was entered into subsequent analyses as a valve-related lethal event. Similarly, mortality resulting from adverse cerebrovascular events was assumed to be valve related. Operative mortality was defined as death within 30 days of surgery. Nonstructural valve dysfunction (NSVD) included any abnormality not intrinsic to the valve itself that resulted in stenosis or regurgitation of the bioprosthesis or hemolysis. Any infection involving the prosthesis was considered infective endocarditis (IE). All patients underwent echocardiography before discharge, at the first postoperative months, and later on a regular basis according to territorial hospital and practitioner preference. Unscheduled echocardiography was performed in the case of new symptoms or unexplained fever. The preoperative logistic EuroSCORE I was calculated for each patient using the prospectively collected data and the algorithm available online (www.euroscore.org). Two patients underwent repeat surgery during the follow-up period before of prosthetic endocarditis and had a new Mosaic valve implanted. For the purpose of the time-to-event analysis, for these patients, the reoperation was considered as the last event attributable to the originally implanted prosthesis. Both patients were re-entered in the follow-up analysis for the new implanted prostheses. Individual patient consent to enter the study was waived, because all data were treated retrospectively and anonymously. Additionally, the present data set was registered within the CLIN online database (*Commission Nationale de l'Informatique et des Libertés* [National Committee for Informatics and Freedom]) under the dossier number 1207754, in accordance with French law.

No major changes were introduced in our surgical or anesthesiology protocols during the inclusion period. The aortic valve was accessed in all cases by full median sternotomy, complete cardiopulmonary bypass, and cardioplegic arrest. All bioprostheses were implanted using U-shaped, interrupted sutures in a supra-annular configuration. Postoperative management included lifelong treatment with lysine acetylsalicylate, 160 mg/d. No oral anticoagulant treatment was given in the early postoperative months, otherwise indicated on the basis of coexisting clinical conditions (ie, atrial fibrillation).

Endpoints

The first study endpoints were overall survival and freedom from SVD at long-term follow-up for patients who received the Medtronic Mosaic porcine valve in the aortic position. The third endpoint was survival free from valve-related adverse events (composite endpoint that included valve-related mortality, SVD, NSVD, IE, and thromboembolic and

hemorrhagic events). To clarify whether the occurrence of valve-related adverse events (ie, SVD) was age-dependent, the analyses were stratified according to patient age at surgery: group 1, younger than 70 years; group 2, 70 to 75 years; group 3, 76 to 80 years; and group 4, older than 80 years. The fourth endpoint was the identification of risk factors for the occurrence of SVD during the follow-up period.

Statistical Analysis

Statistical Analysis Systems software, version 9.33 (SAS Institute Inc, Cary, NC), was used for data storage and analysis. Continuous variables are reported as the mean \pm standard deviation and categorical variables as percentages. An intergroup comparison was conducted using the chi-square test and Fisher's exact test for categorical and continuous variables, respectively. For the time-to-event analysis, both the actuarial (Kaplan-Meier) and the actual (cumulative risks) methods were used.⁸ The analyses were eventually stratified by age group. Opposite Kaplan-Meier curves for the survival estimates were compared using the log-rank statistic. For the purposes of the Kaplan-Meier curves, operative deaths were excluded, and only deaths during the follow-up period were considered. We built a Cox proportional hazards regression model to identify potential predictors of SVD occurrence during the follow-up period. After univariate analysis, all variables attaining an α level of ≤ 0.02 were entered in the model as explanatory variables. The assumptions of Cox regression were checked and met, and the model was tested. A diagnostic performance analysis for the logistic EuroSCORE I in predicting operative mortality was performed by construction of the applicable receiver operating characteristic curve, and the area subtending such a curve was quantified as a measure of discrimination (area under the curve). The α level was 0.05.

RESULTS

In the overall population, the average age was 74.7 ± 6.8 years (median, 75; range, 26-93), 63% of the patients were men, and 41.9% were hospitalized while in New York Heart Association functional class III or IV. Aortic stenosis was the prevalent indication for valve replacement surgery, because aortic regurgitation of 3 to 4 or greater was present in 5.8% of cases. The average preoperative maximum and mean transvalvular gradient was 83.4 ± 21.6 mm Hg and 52.2 ± 15.5 mm Hg, respectively. The average left ventricular ejection fraction was $59\% \pm 12.1\%$. The operative timing was nonelective in 2.1% of the patients, and redo surgery was performed in 3.2% of cases after an average 13.3 ± 6.1 -year interval after primary surgery (previous operations were coronary bypass surgery in 1.8%, aortic valve replacement in 1.3%, and mitral valve replacement in 0.1%). Among the patients who underwent redo aortic valve replacement at the index reoperation, the indications were SVD of a previous bioprosthesis (0.8%), valve thrombosis (0.1%), and IE (0.4%), with the Medtronic Mosaic valve involved in 2 cases of IE. Associated procedures were performed in 19.9% of operations (concomitant coronary bypass in 14.6%, ascending aortic replacement in 3.4%, and other procedures in 1.9%, including a 1.1% rate of concomitant mitral replacement or repair). The nominal diameter of the implanted valve was 19 mm in 4.8% of patients, 21 mm in 28.4%, 23 mm in 44.2%, 25 mm in 19%, and 27 mm in 3.7%. Group 1 included 9.9% of the overall population; group 2, 35.2%; group 3, 35.8%; and group 4, 19.1%.

Operative mortality was 5% and was valve related in 14% of cases ($n = 7$). According to the current recommendations, the valve-related causes of death included stroke in 4 patients, an undetermined cause in 1, and noncerebral (pulmonary) embolism in 2. The leading non-valve-related causes of death were abdominal complications (26%, including peritonitis and mesenteric infarction whose embolic origin was not documented), heart failure in patients with advanced myocardial disease and well-functioning valves (16%), multiorgan failure (14%), and myocardial infarction (14%). Five valve-related nonlethal adverse events (4 cases of prosthetic thrombosis and 1 case of prosthetic endocarditis) occurred. The average logistic EuroSCORE I was $8.6\% \pm 7.8\%$, which globally overestimated the observed mortality. The corresponding receiver operating characteristic area under the curve was 0.7903, indicating adequate, but not optimal, discrimination of this prediction model in our series of aortic valve replacement operations (curve not shown).

The study design is given in Figure 1. Two patients were lost to follow-up; therefore, we had a total of 955 patients and 8122.17 patient-years available for analysis. The average follow-up period was 8.5 ± 3.9 years (longest follow-up, 18.1). At the end of the follow-up period, 583 patients overall had died (61%). Death was valve related in 8.8% (thromboembolic or hemorrhagic events in 19 patients, IE in 7, other adverse cerebrovascular events in 24, and primary valve dysfunction in 1 patient only). Death was cardiac in origin in 25.8% of patients (including valve- and non-valve-related causes). In the overall population, the survival rate at 5, 10, and 15 postoperative years was $79.7\% \pm 1.3\%$, $50.5\% \pm 1.7\%$, and $23.4\% \pm 2.2\%$, respectively. As expected, the overall survival at 15 years was significantly lower among the elderly patients at surgery, because of their lower life expectancy: $47\% \pm 9.3\%$ in group 1, $25.1\% \pm 3.8\%$ in group 2, $21.7\% \pm 3.4\%$ in group 3, and $9\% \pm 3.9\%$ in group 4 ($P < .0001$, Figure 2, A).

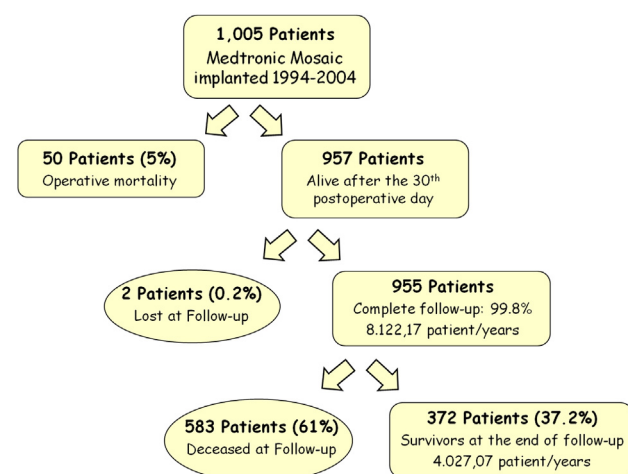


FIGURE 1. Study design. See the text for details.

During the follow-up period, 26 SVD events occurred in 24 patients, and the average interval between surgery and the first SVD event was 9.3 ± 4.9 years. The actuarial freedom from SVD at 5, 10, and 15 years was $99.3\% \pm 0.3\%$, $97.9\% \pm 0.6\%$, and $86.3\% \pm 3.9\%$, respectively. In contrast, the actual method yielded the following corresponding rates: $99.4\% \pm 0.3\%$, $98.5\% \pm 0.4\%$, and $95.1\% \pm 1.2\%$. The freedom from SVD stratified according to age group is listed in Table 1. The actual method described the number of SVD events that factually occurred in the population, and, consequently, the risk to individual patients of incurring an SVD at a given point. The poorer actuarial rates reflected the burden of competing events (death from non-SVD-related causes) that censored the occurrence of SVD. Hence, the risk of developing SVD at 15 years was 10.3% in patients younger than 70 years, 2.9% in patients aged 70 to 75 years, 0.9% in patients aged 76 to 80 years, and 0.6% in patients older than 80 years at implantation. The survival free from SVD was similar among groups 2, 3, and 4; however, the patients in group 1 displayed significantly worse SVD-free survival ($P = .003$, Figure 2, B). Cox proportional hazards regression identified younger age as the only independent predictor of the development of SVD during the follow-up period ($P = .007$). Among the patients who developed SVD, 8 underwent repeat surgery after 9.4 years (mortality rate at reoperation, 12%; average age at reoperation, 67.8 years). The remainder did not undergo reoperation because of excessive estimated surgical risk (8 patients), stable and moderate valve dysfunction resulting from SVD (5 patients), or other or unknown reasons (3 patients). Among the patients who were refused reoperation because of excessive surgical risk, the valve-in-valve procedure was discussed for 4. Of these, 1 underwent valve-in-valve implantation, 2 cases were waived because of unsuitable anatomy and/or unlikely clinical benefit, and 1 was waiting for the final heart team decision. The echocardiographic findings of the explanted SVD prostheses were prevalent stenosis in 3 cases, prevalent regurgitation in 1, and a mixed lesion in 4. Among the nonexplanted prostheses affected by SVD, the findings were prevalent stenosis in 6 cases, mixed lesions in 10, and prevalent regurgitation in none. The pathologic assessment of the explanted bioprosthesis indicated that the mechanism responsible for valve failure was the association of leaflet calcification and tear in most cases (50%), leaflet tear in 25%, and predominant calcification of leaflet and commissures in the remaining 25%. The overall freedom from reoperation for SVD at 5, 10, and 15 years was $99.9\% \pm 0.1\%$, $9\% \pm 0.4\%$, and $95.5\% \pm 2.3\%$ using the actuarial method and $99.9\% \pm 0.1\%$, $99.4\% \pm 0.3\%$, and $98.4\% \pm 0.7\%$ using the actual method, respectively. The freedom from reoperation for SVD according to the age cohorts is listed in Table 2.

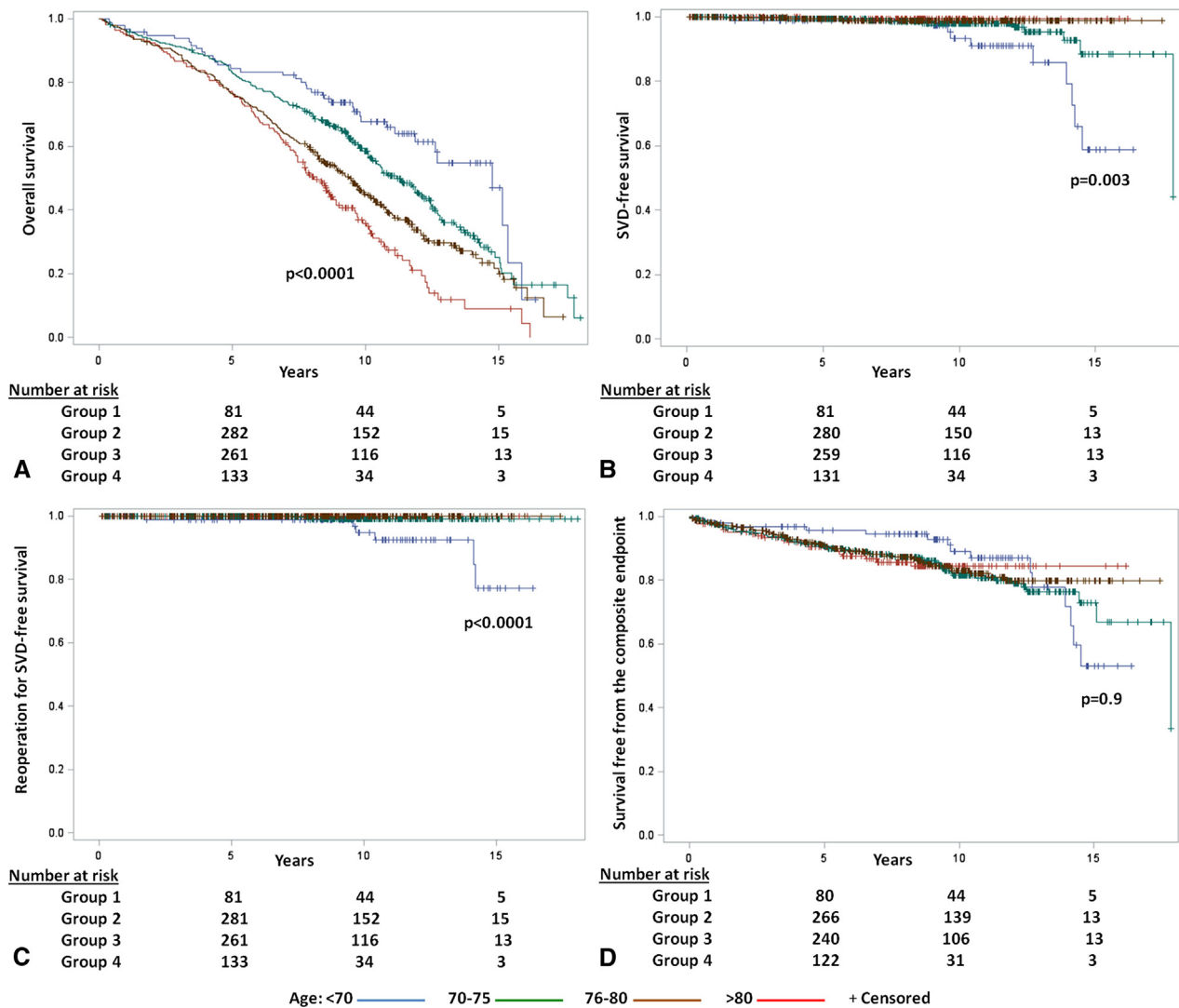


FIGURE 2. Kaplan-Meier curves for follow-up survival, stratified by age group (log-rank *P* values shown). A, Overall survival. B, Survival free from structural valve deterioration. C, Survival free from reoperation for structural valve deterioration. D, Survival free from the composite endpoint. SVD, Structural valve deterioration.

No patient underwent reoperation for SVD in groups 3 and 4 (100% freedom for both). Concordantly, the Kaplan-Meier analysis indicated significantly worse reoperation-free survival in group 1, resulting from the higher SVD rate ($P < .0001$, Figure 2, C). A total of 42 patients (4.2% of the total) were 65 years or younger at surgery.

Among these, we observed 9 SVD events during the follow-up period (21.4%).

Figure 3 shows the SVD-free survival at follow-up stratified according to prosthesis size (19 mm vs the remainder) and postoperative average gradient (<25 vs >25 mm Hg). No significant intergroup differences were found. The

TABLE 1. Freedom from SVD stratified according to age group

Age group (y)	Total patients (n)	SVD events (n)	5-y Follow-up	10-y Follow-up	15-y Follow-up	P value
<70	97	10	98.9 (99; n = 81)	93.3 (94.9; n = 44)	58.8 (75.5; n = 5)	.04
70-75	343	10	99.4 (99.4; n = 280)	98.1 (98.5; n = 150)	88.5 (95.2; n = 13)	.37
76-80	343	3	99.3 (99.4; n = 259)	98.9 (99.1; n = 116)	98.9 (99.1; n = 13)	.98
>80	172	1	99.3 (98.4; n = 131)	99.3 (99.4; n = 34)	99.3 (99.4; n = 3)	Reference
Total	955	24	99.3 (99.4; n = 751)	97.9 (98.5; n = 344)	86.3 (95.1; n = 34)	

Data presented as actuarial rates, with actual rates given in parentheses, followed by the number of patients at risk at each point. SVD, Structural valve deterioration.

TABLE 2. Freedom from reoperation for SVD stratified according to age group

Age group (y)	Total patients (n)	Reoperation events (n)	5-y Follow-up	10-y Follow-up	15-y Follow-up
<70	97	6	98.9 (99; n = 81)	94.8 (96.1; n = 44)	77.1 (86.1; n = 5)
70-75	343	2	100 (100; n = 281)	99.2 (99.4; n = 152)	99.2 (99.4; n = 15)
76-80	343	0	100 (n = 261)	100 (n = 116)	100 (n = 13)
>80	172	0	100 (n = 133)	100 (n = 34)	100 (n = 3)
Total	955	8	99.9 (99.9; n = 756)	99 (99.4; n = 346)	95.5 (98.4; n = 36)

Data presented as actuarial rates, with actual rates given in parentheses, followed by the number of patients at risk at each point. SVD, Structural valve deterioration.

pathologic findings of SVD included the association of leaflet tear and calcification in 4 cases, prevalent calcification and stenosis in 2, and leaflet tear in 2 cases.

Overall, 143 patients (15%) experienced at least 1 valve-related adverse event and, therefore met the composite endpoint. The freedom from the composite endpoint at 5, 10, and 15 years was $91.3\% \pm 0.9\%$, $83\% \pm 1.5\%$, and $71.3\% \pm 3.4\%$ using the actuarial method and $91.9\% \pm 0.9\%$, $86.4\% \pm 1.1\%$, and $82\% \pm 1.6\%$ using the actual method, respectively. No statistically meaningful intergroup differences were found in terms of survival free from the composite endpoint (Kaplan-Meier $P = .9$, Figure 2, D). We observed 8 cases of NSVD, leading to reoperation in 1 case. The actual freedom from NSVD at 15 years was $99.1\% \pm 0.3\%$, without significant intergroup differences ($P = .3$). Of the 66 patients (6.9%) who experienced a thromboembolic event during the follow-up period, 27 died of ischemic stroke (fatality rate, 41%). The overall freedom from thromboembolic events was $92.7\% \pm 0.9\%$ at 15 years (actual method); no significant intergroup difference emerged with the time-to-event analysis ($P = .6$). The global rate of prosthetic endocarditis was 1.6% (15 events, leading to reoperation in 2 cases). The actual freedom at 15 years was $98.2\% \pm 0.4\%$ and without significant intergroup difference ($P = .8$). Finally, the 4 age groups were

comparable with respect to valve-related mortality during the follow-up period ($P = .8$, Figure 4).

DISCUSSION

The Mosaic porcine bioprosthesis was introduced in 1994. It is a third-generation device characterized by glutaraldehyde zero-pressure fixation and antimicrobial treatment with α -amino oleic acid. The durability of this prosthesis in the aortic position has been the subject of previous investigations, which included a maximum follow-up of 13 years in multicenter studies.^{5,9} Surgeons are challenged daily with the choice of the most appropriate valvular substitute (either biologic or mechanical) for individual patients. The anticipated risk of SVD is 1 major determinant of that choice. Therefore, a precise estimation of the expected SVD risk according to the preoperative patient characteristics is of paramount importance. This problem has been previously addressed for second-generation devices.⁶ Nonetheless, it has been suggested that the clinical results at follow-up could be markedly age-dependent for third-generation device.¹⁰

We have presented 99.8%-complete follow-up data for 1007 Mosaic valves implanted during 10 years within 1 institution. The average follow-up duration was 8.5 ± 3.9 years, with a total of 8122.17 patient-years. The assessment

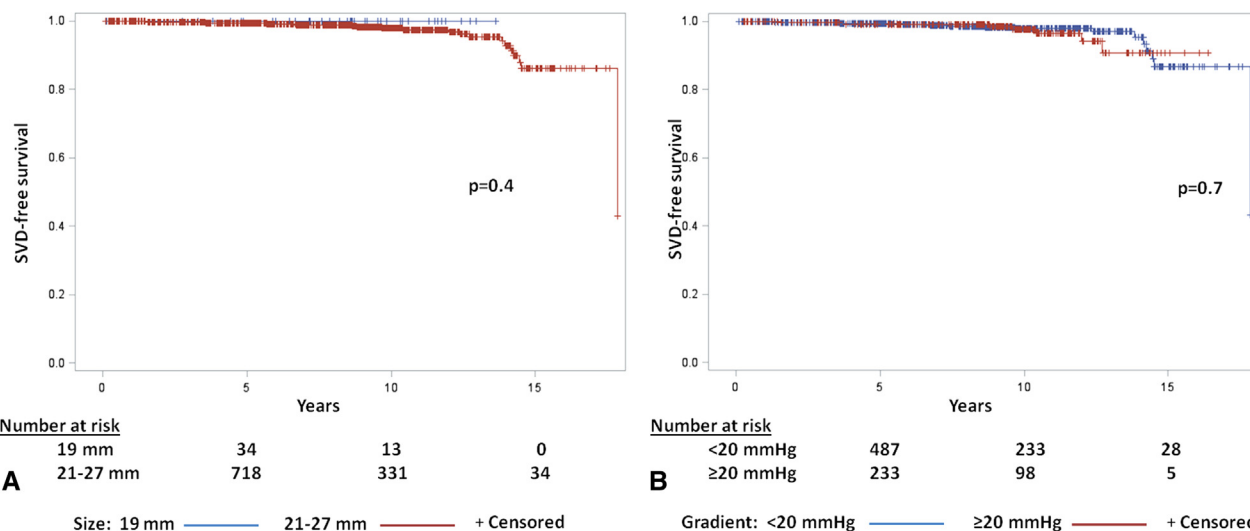


FIGURE 3. Kaplan-Meier curves for follow-up survival from structural valve deterioration (log-rank P values shown). A, Stratified by average transvalvular gradient at discharge. B, Stratified by prosthesis size (19 mm vs the remainder). SVD, Structural valve deterioration.

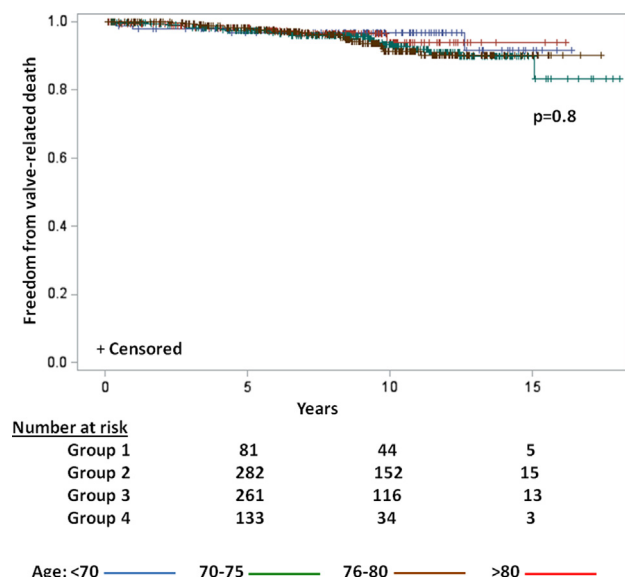


FIGURE 4. Kaplan-Meier curves for follow-up survival, stratified by age group (log-rank *P* values shown). Freedom from valve-related mortality.

of the 15-year outcomes was determined from a relatively limited number of patients attaining this point ($n = 32$), although some patients reached 18 years of follow-up. Nonetheless, previous investigations have based their longest follow-up analyses on similar and even smaller patient cohorts.^{9,10} In the present study, we have reported the largest follow-up period available to date for this prosthesis. Our 86.3% actuarial freedom from SVD at 15 years in the overall population compares well with the 91% actuarial freedom reported at 12 years by Jamieson and colleagues.⁵ Our actual analysis yielded a 95.1% freedom from SVD at 15 years. However, our Canadian colleagues reported a 95.9% actual freedom at 12 years for patients aged 60 years or older at surgery. This finding agrees with the freedom rates of 99.4% to 95.2% we observed in our eldest strata (groups 2-4). Among the younger patients (group 1), we observed a 75.5% actual freedom rate at 15 years versus 80.6% at 12 years reported Jamieson and colleagues.⁵ The comparison of such data is limited by the different distribution of patient age in the 2 populations. The presence in our series of only 29 patients (2.9%) aged 60 years or younger at surgery thwarted the creation of a dedicated age stratum. Also, the definition for SVD used in the study by Jamieson and colleagues⁵ implied demonstration by explant reoperation, and the rates of freedom from reoperation for all valve-related causes were given. This could have led to an underestimation of the rate of SVD compared with our series, in which SVD was defined by preoperative tests with or without explant reoperation. We also specified the freedom from reoperation from SVD only. Only 33% of the patients who received a diagnosis of SVD in our series actually underwent reoperation. Another previous series

reported 89% actuarial freedom from SVD at 13 years, although that study was potentially biased by a limited sample size and the lack of actual analysis.⁹ In other studies, the actuarial SVD freedom rates ranged from 87.1% at 10 years to 96.6% at 7 years.^{11,12} We underline the value of coupling the actuarial and actual methods to address valve-related outcomes. Because SVD is, in most cases, a nonfatal adverse event, the predictions using the actuarial method will be excessively pessimistic for the patient. In fact, death from other causes will censor the occurrence of SVD and related reoperation.⁸ In contrast, the actual rates will consistently clarify the risk of incurring SVD or reoperation during the follow-up period for 1 patient of a given age at the surgical consultation.^{13,14} This issue notably contributes to the choice of an adequate valvular substitute. The importance of the actual (cumulative risk) method increases with an increasing follow-up period and the resulting accumulation of other non-SVD-related fatal events.¹⁵ Therefore, it is relevant for the present study and for similar investigations with even longer follow-up periods.^{6,16}

It has previously been suggested that the rate of prosthetic endocarditis with the Mosaic valve during the follow-up period tends to be increased in younger patients.¹⁰ This concept was not evident in our experience—the actual freedom from prosthetic endocarditis at 15 years ranged from 97.6% to 98.9% among the 4 groups, without statistically significant differences ($P = .8$). Similarly, no other valve-related outcome was age-dependent (NSVD and thromboembolic events), except for SVD and SVD-related reoperation. Patients younger than 70 years presented with increased global rates of SVD, but we did not observe any association between younger age and earlier presentation of SVD (Table 2), similar to the findings for second-generation bioprostheses after equivalent follow-up periods.^{6,17} Nonetheless, the older average age in the present series limited the interpretation, owing to the greater incidence of non-SVD-related lethal events. The relevant number of SVD events in group 1 should be attributed to the patients' longer life expectancy rather than to accelerated deterioration. Additionally, none of the patients in groups 3 and 4 who developed SVD underwent reoperation for this reason, and reoperation was required in 33% of the overall SVD patients. Furthermore, isolated aortic valve repeat replacement is considered to have a lower operative risk than other types of reoperation.¹⁸ However, patients deemed to have excessive reoperative risk might be candidates for the transcatheter valve-in-valve procedure, the indications and technique of which are being increasingly standardized.^{19,20} Finally, despite the increased incidence of SVD in group 1, neither the freedom from any valve-related adverse event (composite endpoint; Figure 2, D) nor the valve-related mortality were statistically different among the 4 groups (Figure 3).

These findings suggest that, although SVD remains a major complication with potentially serious consequences, its effect on the patients' final outcome might be limited in the current era. Additionally, the 15-year actuarial freedom from SVD we observed (86.3%) was almost identical to that found by our group for the Carpentier-Edwards SAV (Edwards LifeSciences, Irvine, Calif) second-generation bioprosthesis (85.9%).⁶

Considerable rates of patient–prosthesis mismatch have been reported for the 19-mm Mosaic prosthesis,²¹ and an association between patient–prosthesis mismatch and SVD has been suggested.²² Although a limited number of 19-mm valves were used in our population (4.8%), no SVD event was recorded among the patients who received the 19-mm prosthesis in our series. Although we did not have enough data regarding the effective orifice area at discharge, stratified survival analysis for freedom from SVD indicated no association between SVD and surrogate markers of patient–prosthesis mismatch. These included the 19-mm prosthesis²¹ and an elevated average transvalvular gradient (Figure 3). This result was confirmed by Cox regression analysis. Chronologic age was confirmed as the sole preoperative factor to discriminate the adequate valve substitute for individual patients. The unavailability of information for the effective orifice area in the entire data set did not allow systematic analysis of its variation over time, a limitation of our investigation. The initial follow-up evidenced that the average transvalvular gradient remained stable or even decreased from hospital discharge to 14 months (from 17.4 to 16.1 mm Hg for prostheses sized 21 mm, from 14.2 to 13.3 mm Hg for prostheses sized 23 mm, unchanged at 10.9 mm Hg for prostheses sized 25 mm, and from 14 to 10.4 mm Hg for prostheses sized 27 mm).²³

As a collateral finding, we observed an overestimation of operative mortality as calculated by the logistic EuroSCORE I (calculated, 8.6%; observed, 5%). The receiver operating characteristic curve analysis indicated adequate, but not very good, diagnostic performance of this risk prediction system.^{24,25} The long-term results achieved through bioprostheses should contribute to the current debate regarding the decision making for high-risk patients affected by severe aortic stenosis.²⁶ The present study was characterized by the prospective collection of in-hospital data and the performance of all operations within the same center, with standardized surgical and clinical protocols. In addition, to the best of our knowledge, this is the largest existing series of Mosaic aortic prostheses. These elements strengthen the reliability of our conclusions. However, the paucity of patients younger than 60 years at surgery was a potential study limitation, and we were unable to provide detailed long-term information for this subgroup. The relatively low number of patients attaining the 15-year follow-up point also should be considered a

potential limitation. Additionally, we lacked sufficient information regarding the anticoagulation status at the thromboembolic and hemorrhagic events during the follow-up period. The present series included patients who had undergone concomitant surgery on the mitral valve; this could theoretically have confounded the assessment of some aortic valve-related adverse events (ie, thromboembolism). Nonetheless, the number of these patients was very limited (1.1%) and predominantly included mitral repair cases. Concomitant procedures were not an exclusion criterion in previous series.^{2,9} As an additional limitation, we lacked data on the radiologic analysis of the prostheses explanted for SVD, because this was not a part of our postexplantation protocols during the study period.

Our data have confirmed the full legitimacy of implanting a bioprosthesis in patients aged 70 years or older. Patients younger than 70 years at of implantation had an increased rate of SVD; nonetheless, the valve-related mortality and other valve-related adverse events were not age-dependent. Implantation of a bioprosthesis in patients younger than 70 years is justified with correct patient information. This should be accomplished using data obtained through the actual method.

The authors are grateful to Mrs Sylvie Marié and Mrs Anne Ingels for their invaluable support in the collection and analysis of the data.

References

1. Thomson D, Jamieson E, Dumesnil J, Busse E, Peniston C, Métras J, et al. Medtronic Mosaic porcine bioprosthesis: satisfactory early clinical performance. *Ann Thorac Surg*. 1998;66:S122-5.
2. Thomson D, Jamieson E, Dumesnil J, Burgess J, Peniston C, Métras J, et al. Medtronic Mosaic porcine bioprosthesis: midterm investigational trial results. *Ann Thorac Surg*. 2001;71:S269-72.
3. Eichinger WB, Botzenhardt F, Gunzinger R, Kemkes BM, Sosnowski A, Maiza D, et al. European experience with the Mosaic bioprosthesis. *J Thorac Cardiovasc Surg*. 2002;124:333-9.
4. Fradet G, Bleese N, Busse E, Jamieson E, Raudkivi P, Goldstein J, et al. The Mosaic valve clinical performance at seven years: results from a multicenter prospective clinical trial. *J Heart Valve Dis*. 2004;13:239-46.
5. Jamieson E, Riess FC, Raudkivi P, Metras J, Busse E, Goldstein J, et al. Medtronic Mosaic porcine bioprosthesis: assessment of 12-year performance. *J Thorac Cardiovasc Surg*. 2011;142:302-7.
6. Ruggieri VG, Flécher E, Anselmi A, Lelong B, Corbineau H, Verhoye JP, et al. Long-term results of the Carpentier-Edwards supraannular aortic valve prosthesis. *Ann Thorac Surg*. 2012;94:1191-7.
7. Akins W, Miller DC, Turina M, Kouchoukos N, Blackstone EH, Grunkemeier G, et al. Guidelines for reporting mortality and morbidity after cardiac valve interventions. *J Thorac Cardiovasc Surg*. 2008;135:732-8.
8. Grunkemeier G, Jin R, Eijkemans M, Takkenberg J. Actual and actuarial probabilities of competing risks: apples and lemons. *Ann Thorac Surg*. 2007;83:1586-92.
9. Celiento M, Ravenni G, Milano A, Pratali S, Sciotti G, Nardi P, et al. Aortic valve replacement with the Medtronic Mosaic bioprosthesis: a 13-year follow-up. *Ann Thorac Surg*. 2012;93:510-5.
10. Riess FC, Bader R, Cramer E, Hansen L, Schiffelers S, Wallrath J, et al. The Mosaic porcine bioprosthesis: role of age on clinical performance in aortic position. *J Thorac Cardiovasc Surg*. 2011;141:1440-8.
11. Riess FC, Bader R, Cramer E, Hansen L, Kleijnen B, Wahl G, et al. Hemodynamic performance of the Medtronic Mosaic porcine bioprosthesis up to ten years. *Ann Thorac Surg*. 2007;83:1310-8.

12. Gansera B, Botzenhardt F, Guzinger R, Spiliopoulos K, Angelis I, Kemkes BM. The Mosaic bioprosthesis in the aortic position: seven years' results. *J Heart Valve Dis.* 2003;12:354-61.
13. Grunkemeier G, Takkenberg J, Jamieson W, Miller DC. Reporting "actual freedom" should not be banned. *J Thorac Cardiovasc Surg.* 2008;135:460-2.
14. Bodnar E, Blackstone EH. Editorial: an "actual" problem: another issue of apples and oranges. *J Heart Valve Dis.* 2005;14:706-8.
15. Grunkemeier G, Takkenberg J, Jamieson W, Miller DC. In response to: Bodnar E, Blackstone EH. Editorial: an "actual" problem: another issue of apples and oranges. *J Heart Valve Dis.* 2006;15:305-6.
16. Jamieson W, Burr L, Miyagashima R, Germann E, MacNab JS, Stanford E, et al. Carpentier-Edwards supra-annular aortic porcine bioprosthesis: clinical performance over 20 years. *J Thorac Cardiovasc Surg.* 2005;130:994-1000.
17. Corbineau H, De Latour B, Verhoye JP, Langanay T, Lelong B, Leguerrier A. Carpentier-Edwards supraannular porcine bioprosthesis in aortic position: 16-year experience. *Ann Thorac Surg.* 2001;71(Suppl 5):S228-31.
18. Luciani N, Nasso G, Anselmi A, Glioca F, Gaudino M, Girola F, et al. Repeat valvular operations: bench optimization of conventional surgery. *Ann Thorac Surg.* 2006;81:1279-83.
19. Piazza N, Bleiziffer S, Brockmann G, Hendrick R, Deutsch MA, Opitz A, et al. Transcatheter aortic valve implantation for failing surgical aortic bioprosthetic valve: from concept to clinical application and evaluation (part 1). *JACC Cardiovasc Interv.* 2011;4:721-32.
20. Ruggieri VG, Bedossa M, Verhoye JP. Urgent trans-axillary valve-in-valve procedure using the Edwards 16F expandable introducer [Epub ahead of print]. *Catheter Cardiovasc Interv.* 2012 Nov 29. doi: 10.1002/ccd.24771.
21. Kirsch ME, Tzvetkov B, Vermes E, Pouzet B, Sauvat S, Loisan D. Clinical and hemodynamic performance of the 19-mm Medtronic Mosaic bioprosthesis. *J Heart Valve Dis.* 2005;14:433-9.
22. Flameng W, Herregods MC, Vercalsteren M, Herijgers P, Bogaerts K, Meuris B. Prosthesis-patient mismatch predicts structural valve degeneration in bioprosthetic heart valves. *Circulation.* 2010;121:2123-9.
23. Corbineau H, Lelong B, Langanay T, Verhoye JP, Leguerrier A. Echocardiographic assessment and preliminary clinical results after aortic valve replacement with the Medtronic Mosaic bioprosthesis. *J Heart Valve Dis.* 2001;10:171-6.
24. Brown ML, Schaff HV, Sarano ME, Li Z, Sundt TM, Dearani JA. Is the European System for Cardiac Operative Risk Evaluation model valid for estimating the operative risk of patients considered for percutaneous aortic valve replacement? *J Thorac Cardiovasc Surg.* 2008;136:566-71.
25. Ruggieri VG, Roudmane Lenglet N, Anselmi A, Flécher E, Harmouche M, Ingels A, et al. Logistic EuroSCORE I risk analysis in aortic valve replacement reoperation after bioprosthetic replacement. *J Heart Valve Dis.* 2013;22:301-8.
26. Barili F, Pacini D, Capo A, Rasovic O, Grossi C, Alamanni F, et al. Does EuroSCORE II perform better than its original versions? A multicentre validation study. *Eur Heart J.* 2013;34:22-9.